MINIREVIEW

Continuous Infusion of β-Lactam Antibiotics

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INTRODUCTION

Over 40 years ago, several investigators attempted to establish the optimal dosage regimens of penicillin G for the treatment of infections caused by common gram-positive bacteria. In a variety of streptococcal infection models in animals, they showed that the total dose of drug required to cure infection was significantly less if the drug was administered in multiple doses at frequent intervals than if it was administered as a single dose or as multiple doses at widely spaced intervals (18, 20, 37). The aggregate time that active penicillin concentrations were maintained, rather than the magnitude of the concentration, appeared to be the important determinant of efficacy against these infections. As a result, repository formulations of penicillin G, designed to maintain continuous levels of the drug in plasma and tissues for protracted time periods, were used extensively in the early years of penicillin therapy.

Studies with penicillin also demonstrated that removal of staphylococci and streptococci from penicillin exposure is not followed by immediate bacterial regrowth (19, 21, 59). Rather, a lag phase or recovery period, which can last for several hours, is observed. This persistent suppression of bacterial growth supported the development of the intermittent dosing regimens for β-lactam antibiotics that are currently used in clinical practice. The goal of a dosage regimen for each individual β-lactam is to prevent the drug-free interval between doses from being long enough for the bacterial pathogen to resume growth (17).

Although these intermittent dosage regimens seem to work reasonably well in clinical practice, we do not know whether we are overdosing or even underdosing patients with most drugs. The increasing number of immunocompromised patients and the rising incidence of gram-negative bacillary infections have added impetus to the development of dosage regimens that will achieve the most benefit with the least amount of drug. During the past decade, many of the issues about dosing regimens raised by the early penicillin studies have been investigated for newer antimicrobial agents and for pathogens such as gram-negative bacilli. The results of those studies as well as the availability of improved intravenous drug delivery systems for both the hospital and the outpatient settings have rekindled interest in the continuous infusion of β-lactam antibiotics. This minireview summarizes current knowledge on the pharmacodynamic properties of β-lactam antibiotics and their pharmacokinetics, therapeutic efficacies, and adverse effects when administered by continuous intravenous infusion.

RATIONALE FOR CONTINUOUS INFUSION OF β-LACTAM ANTIBIOTICS

The pharmacodynamic properties of antimicrobial agents refer to the relationships between drug concentration and drug activity or toxicity. The major pharmacodynamic parameters used to characterize antimicrobial activity are the MIC and MBC. However, the MIC and MBC reflect only the net drug effects over a fixed time of incubation. The time course of antimicrobial activity is more accurately described by parameters such as the pattern of bactericidal activity and the presence or absence of persistent inhibitory effects on growth following drug exposure (11, 27, 75). It is these latter characteristics of β-lactam antibiotics that provide most of the rationale for continuous infusion of these drugs.

Bactericidal activity. In 1976, Shah and associates (67) proposed three patterns of bactericidal activity for β-lactam antibiotics. The first type, typical of penicillins, is characterized by an initial rise in the killing rate with increasing concentrations, but only until concentrations reach four to five times the MIC. Higher concentrations do not significantly enhance the rate or extent of bactericidal activity. The second pattern, reported to occur with cephalosporins, is characterized by a linear rise in bactericidal activity over a much wider range of concentrations. However, other investigators, including those who used in vitro kinetic models, have found that bacterial killing by cephalosporins is relatively independent of concentration and, therefore, is very similar to the pattern observed with penicillins (10, 11, 31, 55, 56). Much of the alleged enhancement in killing by any of the β-lactams at high concentrations reflects an earlier onset of bactericidal activity, while the subsequent killing rate is unrelated to concentration.

The last pattern of bactericidal activity is characterized by a decreasing rate of killing at higher concentrations. This pattern, often called the "Eagle effect" or the paradoxical effect, was first described by Kirby in 1945 (39). It has been observed for β-lactams with certain strains of staphylococci and streptococci (36). The clinical significance of this phenomenon is very questionable, because there are only two case reports, of patients with streptococcal endocarditis, that have described decreased bactericidal activity with high β-lactam concentrations (26, 28).

The in vivo bactericidal activities of β-lactams also show minimal enhancement with increasing drug concentrations. The extent of bactericidal activity in various tissues, including cardiac vegetations, appears to depend more on the duration of exposure to drug levels above the MIC than on the magnitude of antibiotic concentrations (8, 11, 23, 27). The only exception has been in studies of experimental meningitis by Tauber et al. (69) in which drug levels as high

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as 10 to 30 times the MIC were required to achieve maximum rates of bacterial killing. However, it is not clear from the results of those studies how much of the benefit of high concentrations of β-lactams in animals with meningitis is due to an earlier onset of bactericidal activity.

PAE. The postantibiotic effect (PAE) is the term used to describe the persistent suppression of bacterial growth following antimicrobial exposure (46). Short in vitro exposures of a large number of staphylococci, streptococci, and enterococci to different β-lactams are consistently followed by PAEs of several hours in duration (6, 10, 11, 24, 46, 79). Increasing β-lactam concentrations or lengthening the time of drug exposure prolongs the duration of the PAE up to a point of maximal effect. In general, maximal in vitro PAEs for β-lactam antibiotics with gram-positive cocci occur with 2-h exposures at four to eight times the MIC. Bacteria in the PAE phase produced by β-lactams are also more susceptible than untreated control organisms to rechallenge with sub-MICs and to the antibacterial activity of human leukocytes (47, 57, 58).

In contrast to the pattern with gram-positive cocci, no persistent in vitro growth suppression or very short PAEs are observed for β-lactam antibiotics with gram-negative bacilli, including *Bacteroides fragilis* (6, 7, 10–12, 29–31, 79). Very high concentrations, from 32 to 256 times the MIC, are required to produce even modest PAEs with members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (6, 30, 31). The only exception among β-lactam antibiotics is with carbapenem antibiotics, such as imipenem and meropenem. Concentrations of these drugs near the MIC exhibit PAEs of several hours in duration with gram-negative bacilli, especially *P. aeruginosa* (7, 11, 29).

A variety of animal infection models have been used to demonstrate the in vivo presence or absence of PAEs with β-lactam antibiotics. In general, the occurrence of an in vivo PAE is predicted by in vitro results. However, there are a few exceptions. Penicillins consistently produce PAEs with streptococci and enterococci in vitro, but not in the neutropenic murine thigh model or the rat endocarditis model (34, 77). Furthermore, the alleged in vivo PAE for penicillin with streptococci in the rabbit meningitis model appears to be produced by subinhibitory concentrations; it disappears when β-lactamase is injected into the cerebrospinal fluid (CSF) (70). In contrast to these negative results, an in vivo PAE for penicillin has been observed with streptococci in a tissue-cage model in rabbits (58). Lastly, the in vivo PAE found for imipenem with *P. aeruginosa* in the neutropenic mouse thigh model has not been observed in a rat endocarditis model (33). An adequate explanation for these differences has not yet been determined.

Goal of dosing regimen. The presence of the pharmacodynamic parameters described above indicates that very high concentrations of β-lactam antibiotics in serum and tissue do not result in the more rapid killing of bacteria. Furthermore, as soon as levels fall below the MIC, most pathogens rapidly recover and start to grow again. Only with staphylococci have prolonged in vivo PAEs been consistently observed for β-lactam antibiotics (11, 77). The goal of dosing regimens for β-lactams would be to maximize the time of exposure to active drug levels. The duration of time that levels in serum and tissue exceed the MIC has been shown to be the major pharmacokinetic parameter correlating with the efficacies of these drugs in animal models in which the roles of pharmacokinetic parameters were specifically studied (14, 43, 44, 76).

On the other hand, slowly growing bacteria are less susceptible to the killing and lytic activities of β-lactams than are organisms that grow at optimal rates (35). It has been suggested that the activity of β-lactams against slowly growing bacteria might be enhanced by having a drug-free period during which optimal growth would be reestablished prior to the next drug dose. However, the slow growth commonly observed in vivo appears to result primarily from the restricted availability of iron and other nutrients and should persist even during drug-free periods. Studies in chemostats simulating the low bacterial growth rates observed in vivo have shown that constant β-lactam concentrations near the MIC do cause bacterial killing even in the absence of any detectable lysis (9). The rate of killing per generation was found to be quite constant for a given antibiotic, despite marked variations in bacterial growth rates. In addition, Moreillon and Tomasz (49) have observed with pneumococci that repeated cycles of exposure to high penicillin levels (20 times the MIC) followed by a drug-free period actually selected for lysis-defective mutants. Such mutants were not found following prolonged exposure to penicillin concentrations near the MIC. Therefore, it appears that there are many potential microbiologic advantages and no clear contraindications to the continuous infusion of β-lactam antibiotics and that such therapy might enhance the efficacies of these antibiotics against some organisms.

PHARMACOKINETIC AND TOXICOLOGIC EFFECTS OF CONTINUOUS INFUSION WITH β-LACTAMS

There are limited numbers of published studies which compared continuous infusion and intermittent injection of β-lactams with regard to the rate or extent of tissue penetration or the frequency of adverse effects. The majority of studies on tissue penetration which exist have been performed in animal models and require extrapolation to humans.

Tissue penetration. Peterson and associates (60, 74) measured drug penetration into subcutaneous implanted chambers in rabbits following continuous intravenous infusion or intermittent intramuscular injections of three β-lactam antibiotics. The mean concentrations of cefazolin in the chambers following intermittent injection exceeded those resulting from constant infusion for the first 20 h. By 26 h, however, the concentrations in the chambers in animals receiving continuous infusion were 48% higher than those in animals receiving intermittent injections. The penetration of ampicillin was only slightly greater for continuous infusion than for intermittent injection. For oxacillin, no difference in the concentrations in the chambers at equilibrium existed between regimens. With both methods, a delay in equilibration between serum and chamber fluid was observed, but equilibration was slower with continuous infusion, especially for the highly protein bound oxacillin.

Barza and colleagues (2) and Bergeron and colleagues (3, 4, 42) have used subcutaneously implanted fibrin clots and paper disks in rabbits to assess the tissue penetration of five β-lactams (penicillin, ampicillin, cefuroxime, aztreonam, and moxalactam) administered by intermittent injections or continuous infusion. In general, the amount of drug delivered to the interstitial fluid, as measured by the area under the concentration-versus-time curve (AUC), was greater for intermittent injections or a single bolus injection than for constant infusion. However, much of the difference between regimens was reduced when animals were given an initial bolus dose prior to continuous infusion.

In human volunteers, Mouton and colleagues (50, 51) have

used suction-induced skin blisters to compare the extravascular penetrations of ceftazidime and imipenem when administered by continuous infusion or intermittent injection. The AUC of drug in blister fluid with continuous infusion (following a loading dose) was 84.5 to 87.1% of that in serum and was comparable to the AUC following bolus administration. Similar findings have been observed for the penetration of cephaloridine into wound fluid of dogs following a large bolus injection or a small loading dose followed by constant infusion (22). Although peak concentrations in wound fluid were higher following a single large injection, the overall extent of penetration was similar in both cases.

Thus, with continuous infusion, a delay in drug equilibration to tissues occurs because of the lag time for the concentrations in serum to reach steady state. Much of this delay can be reduced by administering a loading dose prior to continuous infusion. After equilibrium occurs, the extent of tissue penetration following continuous infusion appears to be similar to that following intermittent injection.

Penetration into CSF. Plorde and colleagues (61) administered penicillin G to dogs with aseptic meningitis either as three injections given 2 h apart or as a continuous infusion. After 30 min, penicillin levels in CSF were higher following intermittent dosing. However, subsequent samples showed a decline in penicillin levels in CSF with intermittent injections and a gradual increase with continuous infusion. Over the 6-h study period, a larger amount of penicillin G reached the CSF when the drug was administered via continuous infusion. In contrast, Sande and colleagues (64) treated rabbits with pneumococcal meningitis with penicillin G administered as two injections administered 4 h apart or as a continuous infusion. When peak and trough levels in serum and CSF from the two dosing regimens were compared, it appeared that a higher percentage of penicillin was delivered to the CSF by the intermittent injection. However, 18 of 28 samples obtained for determination of trough levels in the CSF of rabbits treated with intermittent injections had undetectable levels of penicillin, whereas none of 28 samples in rabbits receiving continuous infusion did. Syrogiannopoulos et al. (68) administered ticarcillin-clavulanic acid to rabbits with gram-negative bacillary meningitis. Levels of both drugs in CSF averaged 24 to 35% of those in serum following continuous infusion and were equal to the values observed after bolus injection. In another study performed in rabbits, Kern (38) reported that the levels of piperacillin in CSF averaged 16.6% of the levels in serum after continuous infusion.

In the only study performed in humans, Marmo et al. (45) treated six patients who had purulent meningitis with amoxicillin by continuous intravenous infusion. All patients responded to therapy. Concentrations of amoxicillin in CSF averaged 30 to 34% of those in serum. Thus, it appears that adequate delivery of β-lactams into CSF may be accomplished when these agents are administered via continuous infusion and that this method is not inferior to intermittent injection.

Adverse effects. Neftil and associates (52–54) have studied the effect of penicillin degradation during storage or prolonged infusions on the incidence of adverse reactions. They observed that the formation of antipenicillin antibodies and the sensitization of lymphocytes to penicillin in patients could be largely eliminated if doses were prepared just prior to administration. They also monitored the type and frequency of reactions in patients receiving penicillin as a continuous infusion or as bolus doses of stored drug and compared them with those in patients who later received freshly prepared bolus doses. Adverse reactions were classified as definite if the reaction reappeared on repeated exposure and as probable if other drugs could be excluded as a possible cause and rechallenge was not performed. In 193 patients who received penicillin by continuous infusion or as bolus doses of stored drug, the incidences of definite and probable reactions were 8.3 and 6.7%, respectively. In 116 patients who received freshly prepared penicillin, the incidences of adverse reactions were 0.9 and 1.7%, respectively, for definite and probable reactions. In none of the clinical studies which have simultaneously compared continuous infusion with intermittent injections of β-lactams has any difference in the frequency of adverse reactions been reported.

The emergence of resistant bacteria during therapy is another type of untoward effect that can complicate therapy with β-lactam antibiotics. White et al. (78) used an in vitro kinetic model to study the impact of different dosing regimens on the activity of ampicillin against *Escherichia coli*. They found that the AUC or total dose of drug, rather than the method of administration, is more important in preventing the emergence of resistance.

EFFICACY IN ANIMAL MODELS

There are a number of studies in animal models comparing the efficacy of continuous infusion of β-lactam antibiotics with that following intermittent injection (1, 3, 4, 25, 32, 42, 62, 63, 71). Since continuous infusion is technically difficult in small animals, some investigators have instead compared the efficacy of dosing of antibiotics every 1 to 2 h with dosing every 6, 8, or 12 h (13, 14, 17, 43, 44, 48, 65, 66, 72, 73). Many studies have established dose-response relationships that allow for comparison of the potencies of β-lactams from different methods of administration. The amount of drug required to protect 50% of animals from death (50% protective or effective dose) or to reduce bacterial numbers so that they cause 50% of the maximal effect are the usual end points determined.

Against streptococci in normal, immunocompetent animals, the potency of penicillin given by continuous infusion or frequent administration is very similar to that observed with intermittent administration (Fig. 1). Only with dosing of penicillin every 12 h in a rat peritonitis model was the potency of frequent drug administration significantly reduced (66). In contrast, the potency of penicillin against streptococci in the thighs of neutropenic mice and in the lungs of cobra venom-treated rats was more than eightfold greater with continuous infusion or dosing every 1 h than it was with administration every 6 to 12 h (1, 11).

Treatment studies of experimental endocarditis caused by enterococci or *Staphylococcus aureus* treated by continuous infusion have produced conflicting results. Thauvin et al. (71) found continuous infusion of ampicillin to be more effective than repeated intramuscular injections in sterilizing enterococcal vegetations in rats. On the other hand, Hellinger (32) observed no difference in efficacy against enterococcal endocarditis in rabbits when ampicillin was administered either by continuous infusion or by intermittent injection. In both of those studies, the doses administered by continuous infusion produced levels in serum that were four to eight times the MBC. Gengo et al. (25) actually found continuous infusion of methicillin to be less effective than intermittent (every 4 or 8 h) dosing regimens in a staphylococcal endocarditis model in rabbits. However, by continuous infusion the dose of methicillin used produced concen-
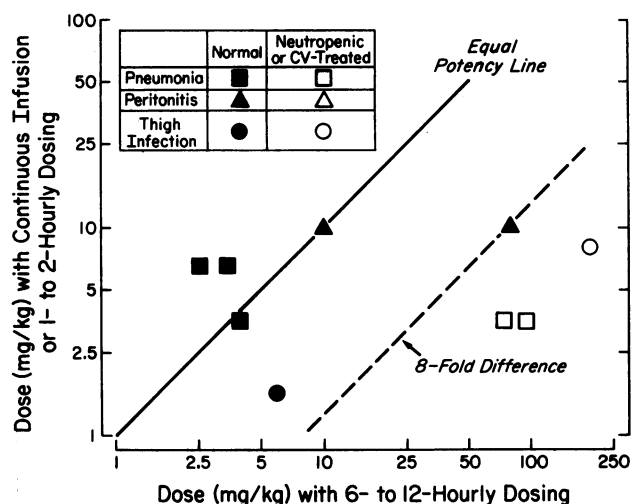
FIG. 1. Comparison of doses required to produce 50% maximal efficacy when penicillin G is administered by continuous infusion or short (1- to 2-h) dosing intervals versus those with longer (6-, 8-, or 12-h) intervals in various streptococcal infections in normal and immunodeficient animals. Data were obtained from references 1, 11, 17, 65, and 66.

trations in serum that were similar to the MIC and slightly less than the MBC. The efficacies of higher doses of methicillin were not studied in that model.

In contrast to the data obtained with gram-positive cocci, continuous infusion of β-lactams has consistently exhibited greater potency than intermittent administration for members of the family Enterobacteriaceae and P. aeruginosa (Fig. 2). Continuous infusion or frequent dosing of the various β-lactams was usually at least eightfold more active than intermittent injections. With continuous infusion or hourly dosing, 90 to 100% maximal efficacy was obtained with antibiotic levels that were only one to four times the
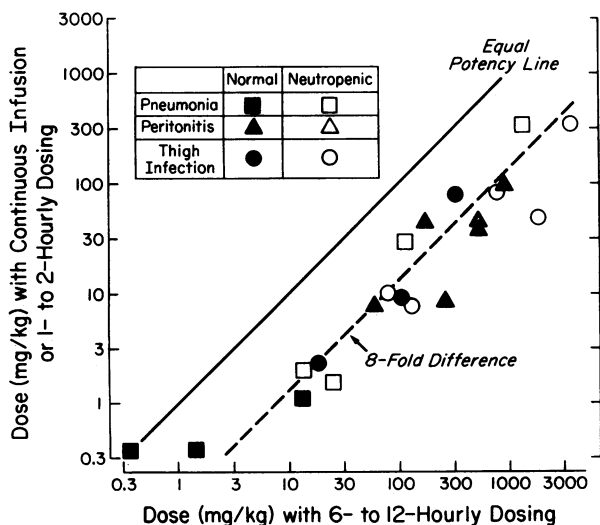

FIG. 2. Comparison of doses required to produce 50% of maximal efficacy when six cephalosporins, ticarcillin, and imipenem are administered by continuous infusion or short (1- to 2-h) dosing intervals versus those with longer (6-, 8-, or 12-h) intervals in various experimental infection models with Klebsiella pneumoniae, E. coli, and P. aeruginosa in normal and immunodeficient animals. Data were obtained from references 13, 43, 44, 62, 63, and 73.

MIC. A single report (62) demonstrated that the two dosing regimens had equal potencies against a Klebsiella pneumonia model in normal rats in which therapy with ceftazidime was initiated within 5 h of organism inoculation. In many of the very same models, no difference in efficacy or potency was observed for aminoglycosides and fluoroquinolones when different dosing regimens were compared (11, 43, 44, 76).

In rabbits with subcutaneously implanted fibrin clots infected with Haemophilus influenzae, Bergeron and associates (4, 42) have observed that bolus administration of β-lactams is more effective in reducing bacterial numbers over 24 h than continuous infusion is. However, a loading dose prior to constant infusion eliminates almost all of the differences in efficacy.

Lastly, the impact of different dosing regimens on the efficacies of β-lactams used in combination with aminoglycosides has been studied in two experimental animal models. Using a Pseudomonas thigh infection in neutropenic mice, Totsuka et al. (72) observed in vivo synergy and greater efficacy when the β-lactam component of the combination was administered by frequent (hourly) doses than when it was administered by intermittent (every 4 or 12 h) injections. Similar finding were observed in a Pseudomonas peritonitis model in neutropenic rats (48).

CLINICAL STUDIES OF CONTINUOUS INFUSION OF β-LACTAMS

Treatment with β-lactam antibiotics by continuous infusions has resulted in good clinical efficacy in a variety of patients, including those with neutropenia who failed therapy with intermittent dosing and those with cystic fibrosis infected with P. aeruginosa (15, 16, 40). Despite these successes, there are only two randomized human clinical trials that have compared the efficacies of β-lactams administered either by continuous infusion or by intermittent injection (Table 1). Both studies involved patients with gram-negative bacillary infections. In one study in which 45 bacteremic patients were treated with cefoperazone, continuous infusion and intermittent dosing were found to be equally effective (39). However, it is impossible to tell from the data whether the group receiving the intermittent (every 12 h) regimen ever had levels of drug that fell below the MIC. In the other study, Bodey et al. (5) compared the efficacies of intermittent versus continuous administration of cefamandole in combination with intermittent carbenicillin in mainly neutropenic patients with infections at various sites. Although that study demonstrated a slightly higher response rate with the constant-infusion regimen, the difference between the study groups was not statistically significant. However, when one analyzes separately the patient subgroups of those infected with cefamandole-susceptible organisms or those with marked neutropenia that persisted during therapy, a significant benefit of continuous administration of cefamandole was observed. The small numbers of patients in the subgroups reduces the importance of this finding.

CONCLUSIONS

The studies included in this minireview demonstrate many potential advantages to the administration of β-lactams by continuous infusion, especially for gram-negative bacillary infections. The administration of a loading dose prior to continuous infusion would eliminate the only potential phar-

TABLE 1. Effect of continuous infusion versus that of intermittent dosing of β-lactams on the outcome of therapy
in patients with gram-negative bacillary infections[a]

Drug or group	Proportion of neutropenic patients included	Method of administration	No. with favorable response/total no. tested (%)	P value
Cefoperazone	11%	Continuous	14/20 (70)	NS[b]
		Intermittent	20/25 (80)	
Cefamandole with intermittent carbenicillin	72%	Continuous	48/74 (65)	NS
		Intermittent	52/92 (57)	
Subgroups				
Cefamandole-susceptible organisms	Most	Continuous	22/24 (92)	0.04
		Intermittent	19/30 (63)	
Persistent neutropenia	All	Continuous	13/20 (65)	0.03
		Intermittent	3/14 (21)	

[a] Data are from references 5 and 41.
[b] NS, not significant.

macokinetic disadvantage of continuous infusion and ensure the rapid onset of antibacterial activity. This form of drug administration would be most suitable for β-lactams with rapid elimination half-lives that currently require frequent intermittent dosing to maintain concentrations in serum and tissue greater than the MIC for most of the dosing interval. Continuous infusion may also allow for the use of lower daily drug dosages than those required for intermittent administration. For example, the daily dose of ceftazidime needed to produce levels in serum and blister fluid greater than 4 μg/ml at all times would be 75 mg/kg of body weight with an 8-h dosing regimen but would be only about 20 mg/kg with continuous infusion (50). Further clinical trials are needed to clearly establish the benefits, as well as any disadvantages, of continuous infusion of β-lactams over current intermittent dosing regimens.

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